UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,681	07/20/2001	Gregory R.D. Evans	UTSC:646US	2530

7590 11/28/2003

FULBRIGHT & JAWORSKI L.L.P.
A REGISTERED LIMITED LIABILITY PARTNERSHIP
SUITE 2400
600 CONGRESS AVENUE
AUSTIN, TX 78701

EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,681	EVANS ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- Th MAILING DATE of this communicati n app ars on th cover sh et with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *25-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2/11/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *ids 6/17/2002.*

DETAILED ACTION

This office action is in reply to a response to a Restriction Requirement filed 8/11/2003. Applicant's election without traverse of Group I (claims 1-24) in the Paper filed 8/11/03 is acknowledged. An IDS filed 2/11/02 and an IDS 6/21/02 have been identified and the documents considered. The signed and initialed PTO Form 1449s have been mailed with this action. Claims 1-46 are pending. Claims 25-46 are withdrawn.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, there are sequences disclosed on page 48, line 12-13 and page 51, line 28-29 that do not have SEQ ID numbers associated with them. It would be remedial to include the appropriate SEQ ID NO's. If the sequences are not in the Sequence listing, a substitute sequence listing, CRF and statement that the two are the same and include no new matter should be submitted.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It was not executed in accordance with either 37 CFR 1.66 or 1.68. Specifically, Greg Evans signature is not accompanied by a date.

Claim Objections

Claim 5 is objected to because of the following informalities: in line 3, neurotrophin is misspelled.

Claim 14 recites "is by is" which is unclear. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 9, 11-12 and 19-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is vague and indefinite in that the metes and bounds of the cells which are "fibroblast cells, stem cells, fat cells, Schwann cells, astrocytes, endothelial cells and ex vivo propagated nerve cells" are unclear. It is unclear if the cells are all part of the same conduit or whether they are used individually.

Claim 9 and 11-12 are vague and indefinite in that the metes and bounds of the term, a "cell kill gene that is an enzyme" or "thymidine kinase" or "a toxin" are unclear. Genes *encode* enzymes or thymidine kinase or toxins but are not actually any of these gene products.

Claims 19-24 recites the limitation "the induction" in claim 6. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claims read on a broad genus of cell kill gene.

The written description requirement for a genus claim may be satisfied through sufficient description of a relevant a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics such as structure or other physical and/or chemical properties, by functional characteristics couple with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, applicants do not enclose any cell kill genes except to recite that the cell kill gene encodes thymidine kinase, an enzyme or a toxin. The genomic version of any cell kill gene is not disclosed by the specification nor does the prior art apparently disclose the entire gene. Because all of the components of the gene such as regulation sequences, introns, and exons must be determined empirically in order to generate the herbicide tolerance genes, applicant claims the gene without any disclosure about its structure. Furthermore, applicants only recite that the cell kill gene is

thymidine kinase or toxins or enzymes. This recitation is not accompanied by a disclosure of as to the enzymes or toxins envisioned by the invention or the relative properties of the cell kill genes. Therefore, there is no clear description of the structural or functional characteristics required for a cell kill gene as part of the conduit cells. Neither applicant nor the prior art provide a correlation between the structure of the recited cell kill genes and their ability to function in the invention. Given the large size and diversity of cell kill genes and the inability to determine which will also have the essential element, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Claims 1-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The invention recites a conduit comprised of a complex series of compositions for use in a method for in vivo regeneration of nerve tissue. The conduit which is comprised of a biodegradable conduit whose lumen is filled with helper cells that are transformed with an expression vector expressing a growth factor is implanted into a subject to stimulate nerve tissue regeneration. The invention utilizes disciplines of molecular biology and clinical technology.

2) Scope of the invention. The invention recites a complex set of steps with broad scope of subjects. The helper cells can be fibroblasts, stem, fat, Schwann, astrocyte, endothelial and ex vivo propagated nerve cells that have been transformed with a variety of stimulatory growth factors such as nerve growth factor or fibroblast growth factor. Furthermore, the invention envisions the incorporation of a "cell kill gene" into the cells such that upon stimulation the cells are killed. The lack of method steps for use of the invention exacerbates a complex method.

3) Number of working examples and guidance. The specification provides no working examples for the use of the instant invention in humans. Furthermore, in vivo experiments in Sprague-Dawley rats are limited to an analysis of the manufacture characteristics and functional assessments of the material used in the conduits (page 43-48) and to assess the amount of NGF release in vivo (figure 8). There is no exemplary method provided for the use of invention in humans. There are no guidelines, no protocols and no methods that would direct the concentration of vector, dose schedules or means to offset rejection of the conduits.

4) State of Art. Enormous efforts have been directed toward developing potential therapies for nerve regeneration. Much of this work has centered on experimental analysis of methods in Sprague Dawley rats. Conduits have been composed of biological and synthetic

material with little clinical success. The biodegradable polymer conduits of the instant invention have shown good mechanical properties in analysis in rats and to date (see e.g. Widmer et al, Biomaterial, 1998, applicant cited).

5) Unpredictability of the art. The art of nerve repair or regeneration in humans is a high art. The success of the instant invention is highly unpredictable. The use of biodegradable polymers for nerve regeneration was under analysis and showed promise in experimental systems such as Sprague-Dawley rats and in prospective studies. These studies did not involve the inclusion of helper cells transformed with expression vectors for expression of growth factors or cell kill genes. It is not clear that reliance on the experimental models accurately reflects the relative efficacy of the claimed therapeutic strategy.

6) Summary. The invention recites a complex series of methods for regeneration of nerve tissue in humans. The method proposes the grafting of biodegradable conduits filled with cells transformed with expression vectors for the expression of growth factors such that tissue growth is stimulated by the growth factors. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art. In view of predictability of the art to which the invention pertains and the lack of established clinical protocols and the inability to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be

concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-7 rejected under 35 U.S.C. 102(a) as being anticipated by Hadlock et al, US 2001/0031974 A1, see entire document. This rejected is directed toward the use of the method of the instant invention in non-human subjects i.e. rats.

Hadlock et al teach a neural regeneration conduit that is a porous and can be comprised of PLGAS or PLLA (see e.g. paragraph 0005). The conduit includes a layer of cells such as Schwann cells that can be engineered for the over-expression of neutrotropic factors or NGF through recombinant expression (see e.g. 0032). The conduits is implanted into a subject such that it is adjacent to nerve tissues (see e.g. 0039-0040).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hadlock et al, US 2001/0031974 A1 in view of Deculve US 5,888,774, see entire document. This rejected is directed toward the use of the method of the instant invention in non-human subjects i.e. rats.

The invention recites a nerve tissue conduit that is comprised of a biodegradable conduit with helper cells transformed with an expression cassette comprising a promoter active in said cells that directs expression of a growth factor.

Hadlock et al teach a neural regeneration conduit that is a porous and can be comprised of PLGAS or PLLA (see e.g. paragraph 0005). The conduit includes a layer of cells such as Schwann cells that can be engineered for the over-expression of neutrotropic factors or NGF through recombinant expression (see e.g. 0032). The conduits is implanted into a subject such that it is adjacent to nerve tissues (see e.g. 0039-0040). Hadlock et al do not teach the specifics of the vector used in the recombinant generation of the cells that express growth factor.

Deculve et al teach the development of a vector for transformation of cells such as stem cells and fibroblasts (column 13, line 64). The vector contains polyadenylation signals as well as promoters such as CMV and EF1 and supF as a selection marker (figure 7 and 8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the vector of to clone the growth factor for expression of the growth factor in Schwann cells to as taught by Hadlock et al. because Promega teach that it is within the ordinary skill of the art to clone transgenes into the vector for expression in Schwann cells and because Hadlock et al. teach that it is within the ordinary skill of the art to make recombinant Schwann cells. One would have been motivated to do so in order to receive the expected benefit of

efficient expression. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1636

November 21, 2003

GERRY LEFFERS
PRIMARY EXAMINER